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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,353	SENO ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *2 and 4-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received January 14, 2008 are acknowledged.

Claims 1-3 have been amended.
Claims 6-19 have been added.
Claims 4 and 5 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed May 25, 2007.

Newly submitted claims 6-19 as well as claim 2 as amended January 14, 2008 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: A first action on the merits was mailed on September 13, 2007 in which claims 1-3 as they read on compositions comprising eosinophil cationic protein (ECP) were examined. As part of applicant's instant response, applicant has submitted new claims 6-19 which are directed to methods of using ECP products. As such, the new claims and the originally elected invention are related as product and process of use. Note that ECP can be used in various methods, such as methods of making antibodies that bind ECP in addition to those methods recited in the new claims, and as such there is patentable distinctiveness between the inventions. Further note that claim 2 has been amended to recite a method, thus changing its category of invention from a product to a method. As such, claim 2 has been grouped with new claims 6-19 which read on methods of using ECP.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 2 and 6-19 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1 and 3 are under examination as they read on compositions comprising ECP.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising ECF and a pharmacological component, does not reasonably provide enablement for therapeutic compositions comprising ECF and a pharmacological component. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The office action mailed September 13, 2007 states:

> Applicant has claimed compositions comprising ECP and pharmacological components or cell biological components. "Pharmacological" and "cell biological" components are defined on pages 8-11, and include ordinary excipients such as phosphate buffered saline. Applicant has also provided data wherein addition of ECF causes fibroblasts to proliferate (Figure 1), fibroblasts and myocytes to develop more extensive actin cytoskeletons (Figures 5 and 8), and nerve-like PC12 cells to survive cell culture without serum (Figure 11). However, the activity of ECP appears to be cell type specific. For example, Figure 1 demonstrates that ECP induced proliferation in fibroblasts, but other tested cells such as smooth muscle (A10), mammary epithelium (HC-11) and human umbilical vessel endothelium (HUVEC) either did not proliferate or were inhibited in proliferation (HC-11 and HUVEC) as compared to control. The growth of many other cell types is known to be inhibited by ECP, such cell types including carcinomas and leukemias (Maeda et al., see entire document, particularly the abstract).
>
> Further, applicant has recited that the ECP compositions are therapeutic compositions suitable for diseases such as heart, bone and neurodegenerative disease. No in vivo data is disclosed wherein ECP compositions were administered to treat any disease, either in humans or in animal models. The specification appears to base the assertion of therapeutic utility upon the observed effects of administering ECP to cultured cells in vitro. Neuronal tumors are characterized by excessive growth and often a failure of differentiation, with the growth of these cells leading to brain damage and potentially death (Elek et al. and Edsjo et al., see entire documents). As such, a composition that promotes the survival of neurons, which is what the instant specification asserts for ECP compositions, would be contraindicated in such patients. Indeed, applicant's data indicating that ECP promotes survival of a nerve like cell line in serum free condition is surprising given that ECP is well known in the art as a neurotoxin (Rosenberg, see entire document particularly the abstract). The specification does not appear to address this apparent discrepancy concerning the activity of ECP in neuronal tissues. The cytotoxic effects of ECP are known to extend to cell types other than neurons, and ECP mediated destruction of heart muscle has long been reported in the literature (Patella et al. and Rosenberg, see entire

documents). Therefore, while ECP may promote actin skeleton rearrangement in myocytes in vitro, it appears that in vivo the localized effects of ECP in the heart are destructive rather than therapeutic.

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of working in vivo examples, the unpredictability of the art, and the breadth of the claims, a skilled artisan would be required to perform undue trials and errors to make and use the claimed invention.

Applicant's arguments filed January 14, 2008 have been fully considered but they are not persuasive. Applicant argues that the claims have been amended to recite more specific disease conditions and to recite a range of concentrations, thus addressing the issues of record concerning specificity and toxicity since applicant states on page 8 of the response that high concentrations of ECP cause cytotoxicity.

This argument is not persuasive. First, the specification does not indicate specific diseases that are characterized by the recited conditions, such as decreased nerve cell survival, and as such the identity of the diseases for which the therapeutic composition will be administered is unclear. Further, as discussed in the rejection of record, the term "therapeutic" indicates an intended in vivo use and no data concerning diseases in humans or animal models has been provided. Such information is important because it is known in the art that many neuroprotective drugs (i.e. preventing the death of neurons) that demonstrated promising results using in vitro tests and even small animal models were failures in human clinical trials (Chaulk et al., see entire document, particularly the abstract and the first paragraph of the Discussion section on page 480). Given that the art recognizes that in vitro data is not correlated with therapeutic efficacy in clinical trials, and the fact that only in vitro data has been disclosed by applicant, it does not appear reasonable that the claimed compositions are "therapeutic".

Additionally, biologically active substances typically have dose response curves, wherein altering the concentration of a reagent is correlated with a change in the strength of the observed biological response. Note that in Figure 12 which presents data concerning ALP secretion by an osteoblast-like cell line after exposure to ECP, a response similar in magnitude to the positive control (BMP-4) was observed when using the lowest concentration (1ng/ml) while the next higher concentration (10 ng/ml)

inhibited the response and the two highest concentrations (100 and 1,000 ng/ml) were equivalent to the negative control (i.e. no demonstrable effect). No error bars are provided to indicate the reproducibility of these data. Note that the claim preamble recites "decreased osteoblast differentiation". BMP-4 is known to induce osteoblast differentiation and ALP secretion, and it is known that increased ALP activity is correlated with increased osteoblast differentiation (Yamaguchi et al., see entire document). As such, it appears that the lowest tested concentration may increase differentiation, while the next concentration decreases differentiation and the highest tested concentrations have no effect. Thus, the majority of the recited range of "not more than 1 μM ECP" lacks the ability to influence ALP activity in a manner correlated with decreased osteoblast differentiation and as such cannot be used to achieve the goal recited in the claim preamble. Note that the higher concentrations of ECP that show the same results as the negative control are not "therapeutic" because they are equivalent to doing nothing. Other disclosed in vitro data indicates that different concentrations are needed to observe different biological responses when using other types of cells, and as such it appears that biologically effective concentrations empirically vary for different cell types and lines, and as has been discussed previously, in vitro data is not indicative of therapeutic efficacy in vivo.

Further, applicant has argued that the concentration of ECP in the instant claimed products has been reduced to avoid issues of toxicity inherently present in concentrated solutions of basic proteins, such as ECP (see particularly page 8 of the response). However, Tai et al. report that 2 nM ECP was toxic to rat heart cells (see entire document, particularly the middle of the right column of page 1982). As such, it is not clear how compositions comprising ECP will be therapeutic for treating conditions such as immature myocardial muscle fiber and decreased heartbeat when concentrations well below the instant claim threshold of "not more than 1 μM" are known in the art to be toxic.

Therefore, in view of the breadth of the claimed invention, the guidance and direction of the instant specification and the teachings of the art a skilled artisan would

be unable to use the full breadth of applicant's claimed invention without conducting additional research.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. The rejection of claims 1 and 3 under 35 U.S.C. 102(b) as being anticipated by WO 01/85766 (of record) has been withdrawn in view of applicant's claim amendments received January 14, 2008 that recite "a concentration of not more than 1 uM" in both independent claims.

6. The following are new grounds of rejection necessitated by applicant's claim amendments received January 14, 2008

7. Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has amended the independent claims to recite the limitation "a concentration of not more than 1 μM" and points to specific passages in the specification to support such an amendment.

Review of these passages finds support for the specific concentration of 1 μM, but not support for the non-lower bound range of "a concentration of not more than 1 μM" which encompasses every possible concentration from zero to 1 μM. It is noted that lines 22-23 of page 20 disclose additional concentrations as part of a working

example. Such a disclosure of discrete points is not the same as disclosure of a range as is currently recited. Further, these distinct points are disclosed for one particular experiment and are not disclosed generically as applying to all diseases, conditions, and disorders. Therefore, it appears that applicant has amended the claims to recite subject matter that was not disclosed as part of the invention at the time the instant application was filed. In response to this action, it is suggested that applicant either point out where specific support for the range "a concentration of not more than 1 μM" is located in the specification as filed or amended the claims to remove the new matter.

8. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Tai et al. (Biochem J., 1982, 204:75-80).

Tai et al. disclose the administration of compositions comprising ECP to rat heart cells (see entire document, particularly Table 1). The concentrations of ECP added to rat heart cells include 40, 80, 120, and 160 ng/ml. Note that as per page 8 of applicant's response received January 14, 2008, one μM ECP is equivalent to 15.5 μg/ml ECP, and further note that 1 μg = 1,000 ng. As such, the compositions are "not more than 1 μM." These compositions were made by dialysis against a 0.01M EGTA buffer solution (see particularly the right column of page 76), and therefore the resulting composition comprises the buffer EGTA since the dialysis membrane allows for free exchange of the buffer.

The claimed compositions and media are both recited as comprising the same two components, namely ECP and a pharmaceutical or cell biological component. Both "pharmaceutical" and "cell biological" components are disclosed in the instant specification as including buffers (see particularly pages 9 and 11). EGTA is a buffer and therefore it is a "pharmaceutical" and a "cell biological" component. Note that applicant's recited intended use limitations do not alter the structure of the claimed compositions and therefore said intended uses do not serve to distinguish the instant claimed invention from the structures disclosed in the prior art.

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/85766 (of record) as evidenced by the article "Volume of Blood in A Human" edited by Glenn Elert.

The '766 patent discloses ECF in various compositions for the treatment of disease (see entire document, particularly the abstract and page 2). These compositions are disclosed as comprising "cell biological components" such as phosphate-buffered saline and are disclosed for administration by a wide variety of routes such as parenteral, intramuscular, intravenous, subcutaneous, intraocular and transdermal (see particularly pages 20-21). Note that the instant application indicates on page 11 that the term "cell biological component" includes phosphate buffer. Multiple ranges of therapeutic dosages of ECP are disclosed (see particularly lines 1-3 of page 21). ECP is also disclosed as part of cell culture media that is used in assays designed to detect changes in the biological activity of fibroblasts (see particularly pages 26-28).

It is noted that the '766 patent does not appear to disclose the administration of compositions comprising ECP for treating the recited disease symptoms. However, the

structure of the claimed invention is a product consisting of ECP and a pharmacological component. This structure is present in the pharmaceutical compositions disclosed in the '766 patent. As such, the recitation of disease conditions is an intended use limitation that does not distinguish the structure of the claimed composition from the structure disclosed in the prior art.

It is noted that the instant claims recite the limitation range "a concentration of not more than 1 μM" and that applicant has argued that this is why the instant claims are not anticipated by the '766 patent.

The lower bound of one disclosed range of administered ECP (which is disclosed as being delivered intravenously) in the '766 patent is 0.01 mg/kg body weight (i.e. 10 μg/kg body weight). As evidenced by the article "Volume of Blood in A Human", a typical male is 70 kg and has 5 L of blood (i.e. 5,000 ml). As per page 8 of the 1/14/08 reply, 1 μM is equal to 15.5 μg/ml. Therefore:

(10 μg ECP)/(kg body) x 70 kg body = 700 μg

(700 μg /5,000 ml) = 0.14 μM

As such, the range of doses disclosed in the '766 patent overlap with the range recited in the instant claims. As per MPEP 2144.05, in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Further, the courts have held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955) and MPEP § 2144.

11. No claims are allowable.

12. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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